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Original Article

A Study of the Cortisol Levels and the Affected Factors in Pediatric Patients with Congenital Diaphragmatic Hernia

Warangkana Thammasanya, MD
Suranetr Chivapraphanant, MD
Achariya Tongsin, MD

Department of Surgery, Queen Sirikit National Institute of Child Health, Bangkok, 10400 Thailand

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Abstract

Objective: Congenital diaphragmatic hernia (CDH) is one of the most serious diseases in pediatric surgery. The morbidity and mortality associated with CDH are largely due to pulmonary hypoplasia and pulmonary hypertension. Low cortisol levels may be associated with the severity of CDH. The aim of the present study was to study the cortisol levels and evaluate factors associated with cortisol levels in pediatric patients with CDH.

Materials and Methods: A retrospective study was conducted by reviewing the medical records of infants with CDH admitted to the Queen Sirikit National Institute of Child Health (QSNICH) between August 1, 2017 and December 31, 2018. The cortisol levels of these infants were recorded and evaluated to study the factors that may be associated with decreased cortisol levels. A cortisol level that was less than 15 mcg/dl was designated as lower than the normal level. The data was analyzed using the Chi-square, Student t-test, and Pearson correlation methods. A *p*-value of less than 0.05 was considered significant for the purposes of this study.

Results: Twenty-eight infants with CDH (14 males, 14 females) were treated at QSNICH. The ratio of patients with low cortisol levels (< 15 mcg/dl) to normal cortisol levels (> 15 mcg/dl) was 2:1 (19:9). Within both groups, 68% of the infants developed hypotension and a subsequent 70% of these hypotensive patients required additional use of hydrocortisone and inotropic drugs in order to sustain normal blood pressure. Low gestational age was associated with low cortisol levels in these infants ($p = 0.044$). High mean airway pressure and high oxygenation index appear to have some correlation with low cortisol levels. Survival rates between CDH patients with low and normal cortisol groups were not significantly different (73.7% vs. 77.8%; $p = 0.815$), and the overall survival rate of all patients was 75%.

Conclusion: Of the 28 infants with CDH, approximately two-thirds had a low cortisol level. There was an association between low cortisol levels in infants with CDH and higher mean airway pressure and oxygenation index. Hydrocortisone may be used in CDH patients with low cortisol levels and inotrope-resistant hypotension in order to sustain a normal blood pressure.

Keywords: Congenital diaphragmatic hernia, Cortisol levels, Mean airway pressure, Oxygenation index

Introduction

Congenital diaphragmatic hernia (CDH) is a congenital anomaly characterized by failed closure of the diaphragm which allows the abdominal viscera to herniate into the thoracic cavity during prenatal development. The incidence of CDH in Thailand was 1 in every 3,230 live births[1] (based on data from Rajavithi Hospital), which is similar to a recent study in Europe (1 in every 3,400 registered births)[2]. CDH is one of the most severe diseases in pediatric surgery, with a high

Correspondence address: *Suranetr Chivapraphanant MD, Department of Surgery, Queen Sirikit National Institute of Child Health, 420/8 Rajavithi Road, Bangkok, 10400 Thailand; Telephone/Fax: +66 234 8095; Email:* surgeryunit@hotmail.com

morbidity and mortality rate. Although many pediatric surgeons have attempted to develop several treatment modalities. Unfortunately, CDH treatment continues to be unsatisfactory in some cases. The principal causes of death in patients with CDH are pulmonary hypoplasia and persistent pulmonary hypertension of neonates (PPHN)[3].

Currently, CDH is treated through stabilization until the patients reach a near-normal physiologic status before surgical correction[4-6]. From our observations, patients with CDH usually had hypotension during stabilization. Some of these cases responded to intravenous fluid and inotropics (dopamine, dobutamine, adrenaline and levophed) administration. However, some cases did not improve and hypotension persisted until death. Kamath[7] reported adrenal insufficiency in neonates with CDH that had hypoxic respiratory failure and hypotension. Pizarro[8] studied the use of corticosteroids in children with adrenal insufficiency and septic shock, and recorded many benefits and an increased survival rate. As of August, 2017, a policy had been implemented to measure cortisol levels in all patients with CDH who are admitted into our institute. Hydrocortisone was given intravenously in cases with low cortisol levels and inotrope-resistant hypotension. Herein, we purposed research questions regarding cortisol levels in our patients with CDH and analyzed patients' data to determine factors influenced by low cortisol levels.

Materials and Methods

A retrospective study was conducted at the Department of Surgery, Queen Sirikit National Institute of Child Health after the proposal had been approved by the Research Ethics Review Committees of the institute (Document No. 61-081). Medical records of patients with CDH who were treated between August 1, 2017 to December 31, 2018 were reviewed. In cases where there was an inability to clearly distinguish between a diagnosis of CDH or eventration of the diaphragm, including if this was due to incomplete medical data records, were excluded from the study.

All of the patients in this study were referred from other hospitals in Bangkok and other provinces. The first measurement of cortisol levels was done within the first 24 hours after admission during the preoperative stabilization period. The average age for cortisol measurement was 1.92 days. The timing of blood test varied depending on the arrival and admission period of each case. Each patient's data was collected from their medical records. Principal clinical data, such as blood pressure, blood gas, mean airway pressure, and oxygenation index were recorded on approximately the same dates as the measurement of serum cortisol levels. Hypotension in full-term neonates was defined by a systolic blood pressure recorded at less than 60 mmHg[9].

The primary outcome of this study was to denote any potential findings associated with cortisol levels in infants with CDH, which is considered to be a highly stressful disease. Basal morning cortisol levels ranged from 4-18 mcg/ml, and a cortisol of < 4 mcg/dl was the best predictor for severe adrenal insufficiency with 100% specificity and 100% positive predictive value[10]. In this study, we defined cortisol < 15 mcg/dl as a low cortisol level, based on what was utilized in other studies[7,11,12]. The patients were classified into 2 groups: cortisol < 15 mcg/dl as the low cortisol group and cortisol > 15 mcg/dl as the normal cortisol group.

The secondary outcome was to analyze the affected factors in relation to low cortisol levels, including gestational age, birth weight, side of CDH, cardiac anomalies, PPHN and hypercapnia. Other factors that may be associated or affected by low cortisol levels are blood pressure, the use of inotropic drugs, mean airway pressure, and oxygenation index.

The data for this study was analyzed using SPSS version 20 (IBM® SPPS statistic). Comparison between categorical variables was evaluated by Chi-square test, whereas continuous data was compared using the Student t-test. Correlations between cortisol levels and patient data was supported by analysis through Pearson correlation. A *p*-value of less than 0.05 was considered significant.

Results

Twenty-eight infants (14 males, 14 females) with CDH were treated at our institute. All of the patients presented symptoms of respiratory distress within 6 hours after birth. Left to right-sided CDH was noted in 20 : 8 cases (71.4% : 28.6%). Of the 28 cases, their gestational ages ranged from 33 to 41 weeks (mean 37.5 ± 1.8 weeks). Their birth weights ranged from 1,550 to 3,800 gm (mean 2,714.4 ± 486.4 gm).

Cortisol levels ranged from 0.55 to 62.31 mcg/dl. The patients were classified into 2 groups, the low cortisol group and the normal cortisol group. The low cortisol group (cortisol < 15 mcg/dl) consisted of 19

patients (67.9%) with levels ranging from 0.6 to 13.0 mcg/dl. Eight of the 19 cases (28.6%) had a cortisol level of < 4 mcg/dl which is a clear indicator of adrenal insufficiency. The remaining 9 cases (32.1%) were sorted into the normal cortisol group (cortisol > 15.0 mcg/dl). Their cortical levels ranged from 15.6 to 62.3 mcg/dl. Comparison of categorical data between the low and normal cortisol groups revealed no significant difference (Table 1). For the continuous data of the 2 groups, the results revealed significant difference in only one factor, gestational age (Table 2). This seems to suggest that CDH patients with a lower gestational age may be prone to lower cortisol levels.

In Table 3, Pearson correlation was used to convey the correlation between cortisol level and various patient data. We found that cortisol levels had some correlation to mean airway pressure ($p = 0.012$) and oxygenation index ($p = 0.001$) (Figure 1,2). The patients with low cortisol levels needed high airway pressure and a high oxygenation index.

Of the 19 cases with low cortisol levels, 6 (31.6%) had normal blood pressure and 13 (68.4%) developed hypotension. Four of the 13 hypotensive cases were treated only inotropic drugs and their blood pressure recovered to normal levels without the use of steroids. The remaining 9 cases needed both inotropic drugs and hydrocortisone to increase their blood pressures to normal levels. The final outcomes of each subgroup were not statistically different (Figure 3).

Figure 4 conveys a normal cortisol level group (66.7%). Six cases had hypotension, of which 2 cases responded to inotropic drug treatment and 4 cases needed both inotropic drugs and hydrocortisone to maintain their blood pressure. The final results of the treatment were not different between each subgroup.

As for the outcomes of all 28 patients, 21 patients (75%) were alive after stabilization and surgery, whereas 7 patients (25%) had died. Six of the 7 dead patients had died during stabilization. Based on comparison of the final outcomes between the low and normal cortisol groups, there was no statistical difference in survival and mortality (Table 4).

Table 1 Comparison of categorical data between patients with low and normal cortisol groups

	Low cortisol group (N=19) Cases (%)	**Normal cortisol group (N= 9) Cases (%)**	***p*-value**
Side of defect			
Left : Right	13 (68.4) : 6 (31.6)	7 (77.8) : 2 (22.2)	0.609
Patent ductus arteriosus	14 (73.7)	4 (44.4)	0.132
PPHN*	11 (57.9)	3 (33.3)	0.225
Hypotension	13 (68.4)	6 (66.7)	0.411
Inotropic drugs usage	13 (68.4)	6 (66.7)	0.926

* Persistent pulmonary hypertension of neonate

Table 2 Comparison of continuous data between patients with low and normal cortisol groups

	Low cortisol group (N=19) Range (Mean ± SD)	**Normal cortisol group (N= 9) Range (Mean ± SD)**	***p*-value**
Gestational age (weeks)	33-40 (37.0 ± 0.1)	37-41 (38.4 ± 1.7)	0.044*
Birth weight (grams)	1,550-3,800 (2,659.4 ± 25.5)	2,240-3,390 (2,830 ± 522.1)	0.395
Systolic blood pressure (mmHg)	47-90 (64.3 ± 39.2)	44-80 (62.6 ± 12.2)	0.728
Mean arterial pressure (mmHg)	35-70 (49.3 ± 38.7)	30-61 (46.2 ± 10.6)	0.466
pH	7.1-7.5 (7.32 ± 0.2)	7.2-7.5 (7.3 ± 0.1)	0.306
pCO_2 (mmHg)	30.7-107.8 (52.2 ± 4.3)	24.3-51.4 (40.2 ± 19.8)	0.100
Mean airway pressure (cmH_2O)	6.0-21.0 (11.4 ± 2.3)	6.7-18 (10.7 ± 4.9)	0.569
Oxygenation index	1.9-92.7 (18.1 ± 10.9)	2.7-49.6 (10.7 ± 42.2)	0.332

Table 3 Analysis of correlation between cortisol level and various patients' data

Pearson correlation test	*p*-value
Correlation between cortisol level and:	
- Gestational age	0.200
- Birth weight	0.442
- pH	0.780
- p CO_2	0.238
- Systolic blood pressure	0.260
- Mean arterial pressure	0.338
- Mean airway pressure	0.012*
- Oxygenation index	< 0.001*

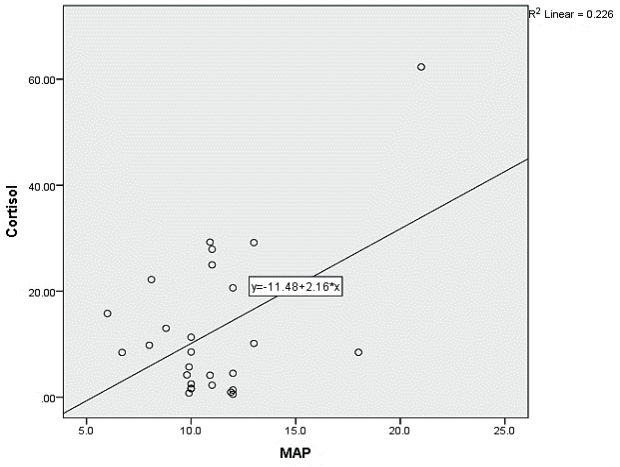

Figure 1 Correlation between mean airway pressure and cortisol level (Cortisol level = 2.16 (MAP)-11.48)

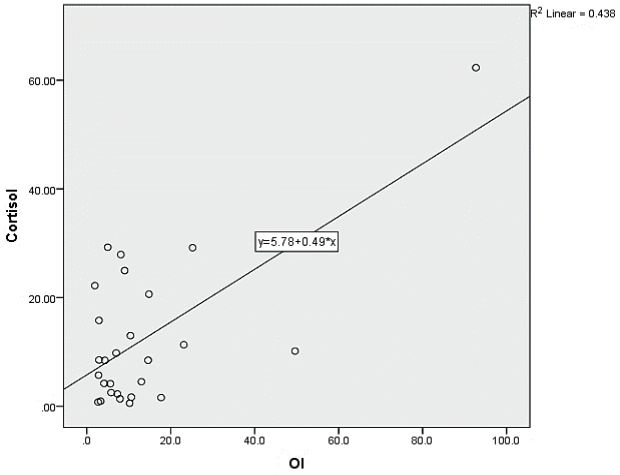

Figure 2 Correlation between oxygenation index and cortisol level (Cortisol level = 0.49 (OI) + 5.78)

Discussion

CDH is one of the most critical and stressful diseases. Twenty-nine percent of our CDH patients had critical adrenal insufficiency (cortisol < 4 mcg/dl). Fernandez[11] had retrospectively studied 673 patients, both term and near-term infants, and found that low cortisol levels affected refractory hypotension and hypoxic respiratory failure. Patients with low cortisol levels responded well to corticosteroid therapy. Several investigators suggested that low critical levels had developed in critically ill and stressed patients because of inadequate adrenal function[11-15]. Sixty-eight percent of the patients had low cortisol levels of < 15 mcg/dl. This result was similar to a previous study by Kamath[7]. Two-thirds of our patients developed adrenal insufficiency, including hypotension and severe respiratory insufficiency, and approximately 70% of these patients required both inotropic drugs and hydrocortisone to raise their blood pressures. Hypotension, seen in some of our patients with normal cortisol levels, did not respond to inotropic drugs. However, their blood pressures increased to normal levels after hydrocortisone administration. Many studies have suggested that corticosteroid therapy has a benefit in children with relative adrenal insufficiency and catecholamine – resistant septic shock[7,8,11,15]. Robertson[16] studied steroid use for refractory hypotension in patients with CDH that had either low or high cortisol levels. He found that adrenal insufficiency was prevalent amongst patients with CDH, but prolonged treatment with hydrocortisone may increase the risk of sepsis and mortality, especially in high cortisol level patients. In our study, there was no statistical difference in mortality according to hydrocortisone use between low and normal cortisol groups.

Through the analysis of factors that may affect cortisol levels, which was based on demographic and clinical data, our data seems to suggest that a low gestational age may be correlated with low cortical levels to a statistically significant degree. Furthermore, low cortisol levels may be related to high mean airway pressure and a high oxygenation index. These findings were interpreted to suggest that patients with CDH that have low cortisol levels had critical respiratory insufficiency and needed high airway pressure with high oxygen support for clinical improvement.

One of the limitations of this study is the relatively small sample size of patients with CDH during the study period. A smaller sample size makes it more difficult to establish potential statistical differences between

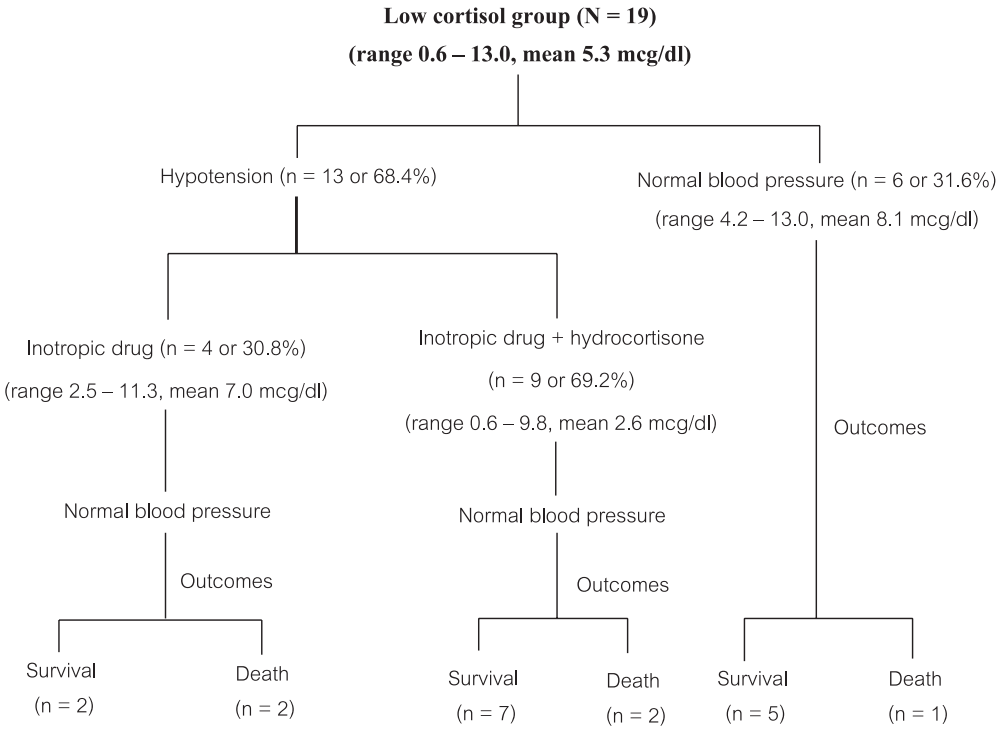

Figure 3 Outcomes of CDH patients with low cortisol level

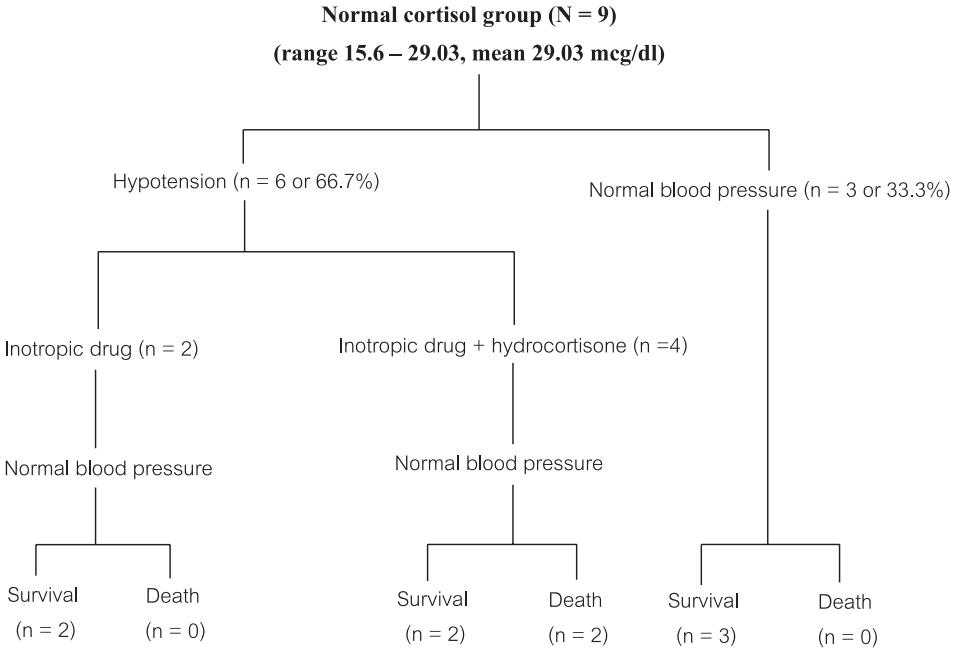

Figure 4 Outcomes of CDH patients with normal cortisol level

factors in both groups. Another potential limitation was that cortisol measurements were not measured at a standardized time. Further studies should be done within an appropriate time period and an adequate number of CDH patients.

Conclusion

In our study, two-third of infants with CDH had a low cortisol level. Based on our findings, low gestational age may play a role in the development of low cortisol levels.

Table 4 Comparison of final outcomes between patients with low and normal cortisol groups

Results	Low cortisol group (N=19) Cases (%)	Normal cortisol group (N= 9) Cases (%)	*p*-value
Stabilization prior to surgery			
- no surgery*	4 (21.1)	2 (22.2)	0.944
- surgery	15 (78.9)	7 (77.8)	
Final			
- survival	14 (73.7)	7 (77.8)	0.815
- death	5 (26.3)	2 (22.2)	

* Death during the period of stabilization

Mean airway pressure and oxygenation index were correlated with serum cortisol levels in CDH patients. Cortisol levels should be measured in severe CDH patients with refractory hypotension. Hydrocortisone should be administered in CDH patients with low cortisol level and inotrope-resistant hypotension in order to increase blood pressure.

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บทคัดย่อ **การศึกษาระดับคอร์ติซอลและปัจจัยที่มีผลต่อระดับคอร์ติซอลในผู้ป่วยเด็กที่เป็นโรคไส้เลื่อนกะบังลมแต่กำเนิด**

วรางคณา ธรรมสัญญา, สุรเนตร ชีวะประภานันท์, อัจฉริยา ทองสิน

กลุ่มงานศัลยศาสตร์ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี กรุงเทพฯ

ความเป็นมา: ไส้เลื่อนกะบังลมแต่กำเนิดเป็นเหนึ่งในโรคที่มีความรุนแรงในกุมารศัลยศาสตร์ ภาวะแทรกซ้อนและการเสียชีวิตของผู้ป่วยไส้เลื่อนกะบังลมแต่กำเนิดส่วนใหญ่เกิดจากการเจริญของปอดไม่เต็มที่และเกิดภาวะความดันสูงในปอด การที่มีคอร์ติซอลอยู่ในระดับต่ำอาจมีความเกี่ยวข้องกับความรุนแรงของโรคไส้เลื่อนกะบังลมแต่กำเนิด

วัตถุประสงค์: เพื่อศึกษาระดับคอร์ติซอลและตรวจสอบหาปัจจัยที่มีผลต่อระดับคอร์ติซอลในทารกที่เป็นโรคไส้เลื่อนกะบังลมแต่กำเนิด

วัสดุและวิธีการ: เป็นการศึกษาย้อนหลังโดยการทบทวนเวชระเบียนของทารกที่เป็นโรคไส้เลื่อนกะบังลมแต่กำเนิด ที่เข้ารับการรักษาในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ระหว่างวันที่ 1 สิงหาคม 2560 ถึง 31 ธันวาคม 2561 ระดับคอร์ติซอลได้รับการรวบรวมและนำไปตรวจสอบเพื่อหาปัจจัยที่มีผลต่อการทำให้คอร์ติซอลมีระดับต่ำ ระดับคอร์ติซอลที่ต่ำกว่า 15 ไมโครกรัม/เดซิลิตร (mcg/bl) ถูกจัดว่าต่ำกว่าปกติ การวิเคราะห์ข้อมูลใช้โปรแกรม SPSS หาความแตกต่างและความสัมพันธ์ด้วย Chi-square, Student *t*-test และ Pearson correlation ค่า *p*-value น้อยกว่า 0.05 แสดงว่ามีความแตกต่างอย่างมีนัยสำคัญทางสถิติ

ผลการศึกษา: ทารก 28 รายที่เป็นโรคไส้เลื่อนกะบังลมแต่กำเนิด (ชาย 14 ราย หญิง 14 ราย) อัตราส่วนของผู้ป่วยที่ระดับคอร์ติซอลต่ำ (< 15 mcg/dl) ต่อผู้ป่วยที่คอร์ติซอลระดับปกติ (> 15 mcg/dl) เท่ากับ 19 : 9 ราย (ร้อยละ 67.9 : 32.1) ร้อยละ 68 ของผู้ป่วยทั้งสองกลุ่มมีภาวะความดันโลหิตต่ำ และร้อยละ 70 ของผู้ป่วยที่มีความดันโลหิตต่ำเหล่านี้ต้องได้รับยา hydrocortisone เพิ่มขึ้นจาก inotropic drugs ที่ให้อยู่แล้ว จึงสามารถเพิ่มความดันโลหิตให้เป็นปกติได้ การวิเคราะห์ข้อมูลต่างๆ ของผู้ป่วย พบว่าทารกที่เกิดจากอายุการตั้งครรภ์น้อย อาจมีผลต่อการมีระดับคอร์ติซอลต่ำ ($p = 0.044$) ผู้ป่วยที่ต้องใช้ mean airway press สูง และค่า oxygenation index สูงมีความสัมพันธ์กับระดับคอร์ติซอลต่ำ ผลการรักษาพบว่าผู้ป่วยกลุ่มที่มีระดับคอร์ติซอลต่ำและกลุ่มที่มีระดับคอร์ติซอลปกติมีอัตราการมีชีวิตรอดไม่แตกต่างกัน (ร้อยละ 73.7 : 77.8; $p = 0.815$) อัตราการมีชีวิตรอดในผู้ป่วยทั้งหมดคือ ร้อยละ 75

สรุปผลการศึกษา: สองในสามของทารกที่เป็นโรคไส้เลื่อนกะบังลมแต่กำเนิดมีระดับคอร์ติซอลต่ำกว่าปกติ mean airway pressure และ oxygenation index มีความสัมพันธ์กับผู้ป่วยที่มีระดับคอร์ติซอลต่ำ กว่าปกติ Hydrocortisone ควรจะได้รับการใช้ในผู้ป่วยไส้เลื่อนกะบังลมที่มีระดับคอร์ติซอลในเลือดต่ำ และมีความดันโลหิตต่ำที่ต้านต่อยา Inotrope